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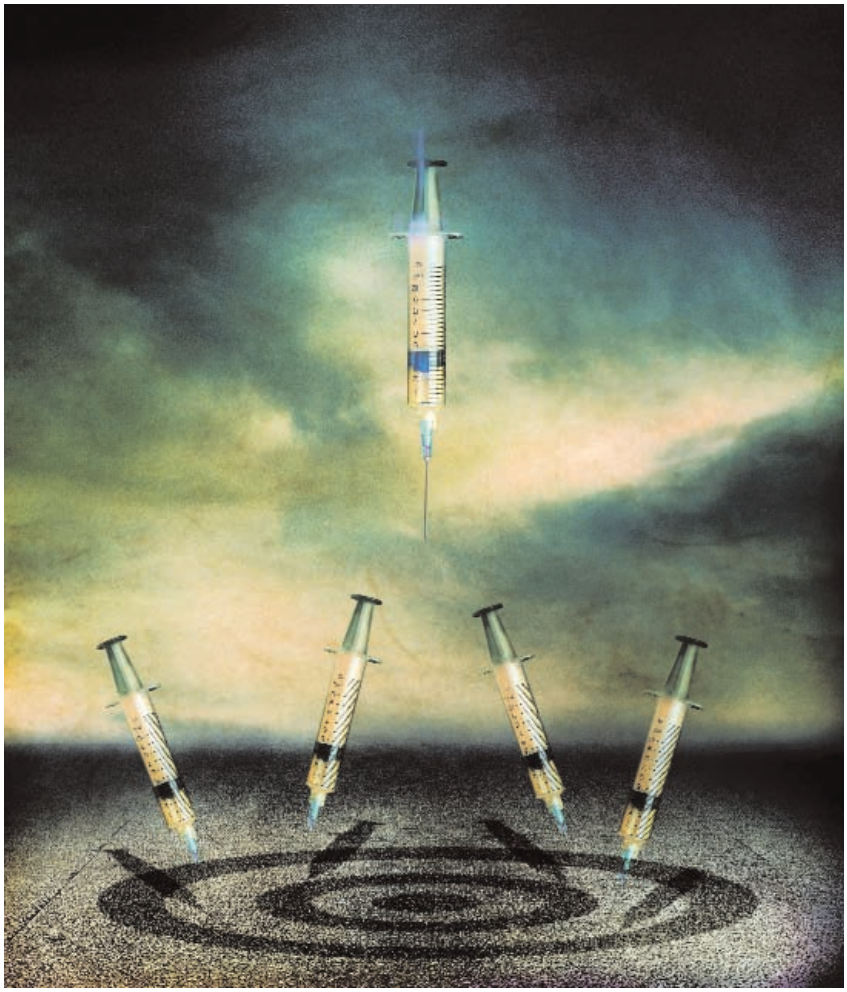
Buprenorphine:

A (Relatively) New Treatment For Opioid Dependence

ABSTRACT

Opioid dependence is a significant and growing problem in the United States. For nearly a century, federal regulations have made it illegal for psychiatrists and other physicians to pharmacologically manage this condition in an office-based setting using opioids. The passage of the Drug Addiction Treatment Act of 2000 has made it possible for all physicians to prescribe buprenorphine to patients in such a setting. Buprenorphine, a partial *mu*-opoid receptor agonist, has unique pharmacologic properties that distinguish it from methadone and other medications used in the treatment of opioid dependence. It has been shown to be as effective as methadone and is generally safe and well-tolerated. It is available in two sublingual formulations: Subutex, which contains only buprenorphine, and Suboxone, which also contains naloxone. Physicians who wish to prescribe either must obtain a special waiver from the federal government and are currently limited to prescribing it for 30 patients at a time.



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INTRODUCTION

Opioid dependence (addiction) is a serious problem in the United States. It is characterized by physiologic dependence (the development of tolerance and withdrawal) as well as a maladaptive pattern of opioid use with impaired control over use, compulsive use, continued use despite harm, and craving (Table 1). According to the National Survey on Drug Use and Health, the incidence of abuse of prescription opioid pain medications (products containing codeine, dilaudid, fentanyl, hydrocodone, hydromorphone, meperidine morphine, oxycodone, oxymorphone, propoxyphene) has risen markedly in recent years with 4.4 million people reporting non-medical use in 2004 (up from 2.8 million in 2000).[1] The same survey found that in 2004, 118,000 individuals in the US used heroin for the first time. In 2003, the Drug Abuse Warning Network reported an estimated 17 percent of drug-related emergency department visits were related to opioid analgesic abuse (36% of the cases specifically seeking detoxification) with eight percent related to heroin use.[2] According to the Office of National Drug Control Policy (ONDCP), there were an estimated 810,000 to 1,000,000 individuals addicted to heroin in the United States in the year 2000.[3] It is believed that a rise in the purity of heroin (from less than 10 percent in the 1970s to between 50 and 90 percent in the 1990s), increased cultivation of poppies in Mexico, and a resultant reduction in price have given rise to new populations of heroin users (including many from the middle and upper classes) as heroin is now easier to use by noninjection routes, such as snorting and smoking.

While opioid use itself can lead to serious medical problems, such as overdose, many of the consequences of opioid use are due to the intravenous route of administration. Common consequences include infection with human immunodeficiency virus (HIV), hepatitis B and hepatitis C, bacterial endocarditis, abscesses, emboli, and septicemia. Additionally, individuals with opioid addiction tend to suffer a progressive deterioration of quality of life. Loss of savings, loss of employment, estrangement from family and friends, and incarceration are frequent social consequences.

Individuals addicted to opioids face many challenges as they battle this disease. Sudden discontinuation of opioids in a dependent patient typically results in an extremely uncomfortable withdrawal syndrome (Table 2). Some of these symptoms, in addition to craving for opioids, may persist for weeks and months after the last use of an opioid. It has been demonstrated that treating all addictions as chronic disorders leads to improved outcomes for patients.[4] Opioid maintenance therapy has been demonstrated to be an effective means to decrease illicit opioid use in addicted patients.[5] In the US, the primary pharmacologic treatment has been methadone. However, access to methadone treatment has been restricted by federal law (The Narcotic Addict Treatment Act of 1974) to highly regulated treatment programs variously referred to as Methadone Programs, Methadone Maintenance

TABLE 1: DSM-IV-TR diagnostic criteria for substance dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12 month period:

1. **Tolerance, as defined by either of the following:**
   a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect
   b) markedly diminished effect with continued use of the same amount of the substance
2. **Withdrawal, as manifested by either of the following:**
   a) the characteristic withdrawal syndrome for the substance
   b) the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms
3. **The substance is often taken in larger amounts or over a longer period than was intended**
4. **There is a persistent desire or unsuccessful efforts to cut down or control substance use**
5. **A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects**
6. **important social, occupational, or recreational activities are given up or reduced because of substance use**
7. **The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.**

TABLE 2: Signs and symptoms of opioid withdrawal

Abdominal Cramping
Anorexia
Anxiety
Diarrhea
Dysphoria
Elevated Blood Pressure
Fatigue
Fever
Headache
Insomnia
Lacrimation
Muscle Spasms
Mydriasis
Myalgia
Nausea
Piloerection
Restlessness
Rhinorrhea
Tachypnea
Tachycardia
Vomitting
Yawning

Programs, Narcotic Replacement Programs, and Opioid Treatment Programs (OTP). These programs typically have stringent entrance criteria and long waiting lists. They are often located in urban areas, and public opposition often makes it difficult for new programs to open. Several states do not have maintenance programs. The combination of the under-availability (approximately 1100 programs nationally), the stigma (with the general public, patients, and healthcare practitioners), and the inconvenience (patients are required to attend a clinic on a daily basis) associated with receiving methadone in the OTP has contributed to the low rate of treatment among patients with opioid addiction. The National Survey on Drug Use and Health found that 283,000 people in the US had received any treatment for heroin dependence in 2004.[1]

Since the Harrison Narcotics Act of 1914, office based-treatment of opioid addiction has not been available in the United States (Table 3). Most physicians have become accustomed to treating the disorders related to opioid addiction (infectious diseases, abscesses, psychiatric sequelae, etc.) but not the addiction itself. The Drug Addiction Treatment Act of 2000 (DATA)[6] has made it possible for physicians to manage opioid-dependent patients with opioid maintenance in an outpatient setting. This act states that a physician can prescribe and a pharmacist can dispense Schedule III, IV, or V "narcotic" medications approved by the Food and Drug Administration (FDA) for the treatment of narcotic-use disorders. In October, 2002, the FDA approved buprenorphine (Subutex®) and a combined formulation of buprenorphine plus naloxone (Suboxone®) for use in the treatment of opioid dependence.

As of the first quarter of 2005, more than 4,500 physicians had obtained the waiver required to prescribe buprenorphine. Approximately two-thirds of these physicians reported that they had actually prescribed the medication.[7]

BUPRENORPHINE

Buprenorphine is a semi-synthetic opioid derived from thebaine, a naturally occuring alkaloid of the opium poppy, *Papaver somniferum*. Buprenorphine is a partial mu receptor agonist originally developed as analgesic but its potential utility for the management of opioid dependence has been discussed since early research in the 1970s.[8] Due to its partial agonist properties, buprenorphine offers some potential pharmacologic advantages over methadone in the management of opioid addiction, such as decreased respiratory depression, less sedation, less withdrawal symptoms, lower risk of toxicity at higher doses, and decreased risk of diversion. There is also the potential for better acceptance by the general public, patients, and healthcare professionals, as well as the ability for physicians to provide more integrated treatment for all medical/psychiatric conditions.

Buprenorphine has three FDA indications: opioid detoxification, opioid maintenance, and pain management. Opioid detoxification describes the process in which a physically dependent individual is gradually tapered off all opioids. Opioid maintenance, on the other hand, is the long-term substitution with a regulated opioid with the goal of decreasing illicit drug use.

Buprenorphine is a DEA Schedule III medication. Under federal law, buprenorphine (Suboxone and Subutex) can only be prescribed for opioid addiction by "qualified physicians" (Table 4). The physician is required to have an active DEA registration and a waiver to prescribe buprenorphine. Buprenex (the parenteral formulation) is not FDA-approved for the treatment of opioid dependence, and its use for that purpose is illegal and may be punishable by law.

Additionally a "qualified physician" must have the capacity to refer patients for appropriate addiction counseling and ancillary services and must certify that he or she will treat no more than 30 patients at one time with buprenorphine. For further information on locations of the required eight-hour course or its online equivalent, see Table 5.

Pharmacology.
Buprenorphine exerts the majority of its effects at the mu

TABLE 3: Select history of pharmacologic treatments for opioid dependence

1860s	Various "cures" for morphine and opium addiction began to appear
1870s	Use of cocaine to treat morphine addiction began
1874	Diacetyl-morphine (Heroin) was synthesized
1898	Heroin was marketed by Bayer for cough; also used to treat morphine addiction
1912	Morphine maintenance clinics began in Jacksonville, Florida
1914	Harrison Narcotics Act: used federal taxation to limit sale/transfer of "narcotics"
1923	Opioid maintenance was outlawed by the US government.
1965	Article published in JAMA describing success of methadone maintenance.
1971	First FDA regulations for Methadone Maintenance
1972	Revision of FDA regulations
1973	Methadone Diversion Control Act
1974	Narcotic Addict Treatment Act (Gave DEA power over storage, licensing, etc.)
1970s	Research with LAAM was conducted; heroin clinics started in UK; first use of clonidine for detoxification
1985	Naltrexone approved in US to treat opioid dependence
1990s	Buprenorphine used for detoxification from opioids; further trials with morphine and heroin maintenance
1993	LAAM approved in the US to treat opioid dependence
1995	IOM report recommending reduced regulations for methadone maintenance
2000	Drug Abuse Treatment Act (Section 3502 of The Children's Health Act of 2000)
2002	FDA approved Subutex and Suboxone
2003	Subutex and Suboxone available in pharmacies
2005	DATA amended: 30 patient per group practice limit lifted

opioid receptor where it acts as a partial agonist. Because of the relatively decreased activation (compared to a full agonist), there is a plateau of receptor activation with no further effect from further increase in dose. This is in contrast with full opioid agonists, such as methadone and heroin, which exert greater opioid receptor activity as the dose is increased (Figure 1). Buprenorphine also has a high affinity for and slow dissociation from mu opioid receptors. This allows buprenorphine to block the effects of other opioids taken after buprenorphine. It also allows the clinical effects of buprenorphine to last significantly longer than would be expected based solely on its elimination half-life.

Buprenorphine is readily absorbed through the gastrointestinal and mucosal membranes. However, due to extensive first-pass metabolism, buprenorphine has very poor oral bioavailability (10% of the intravenous route) if swallowed. Its availability is significantly increased with sublingual administration (30–50% of the intravenous route),[9,10] making this a feasible route of administration for the treatment of opioid dependence. The mean time to maximum plasma concentration following sublingual administration is one hour, ranging from 30 minutes to 3.5 hours. Buprenorphine has a large volume of distribution and is highly protein bound (96%). It is metabolized primarily in the liver via the cytochrome P-450 3A4. The primary products of this metabolism are norbuprenorphine and its conjugate. Norbuprenorphine has little ability to cross the blood brain barrier and so its effects are negligible. The terminal half-life ranges from three hours after intravenous administration to 28 to 37 hours after sublingual administration.[10] It is unclear why there is such a difference in half life depending on the route of administration but this may be related to sequestring of buprenorphine in the oral mucosa. Most of the buprenorphine is eliminated in the feces, with approximately 10 to 30 percent excreted in urine.[11]

In addition to the primary effects on the mu opioid receptor, buprenorphine also appears to act as an antagonist at the kappa opioid receptor (possibly involved with spinal analgesia and antidysphoric effects), as an

agonist at the delta receptor (clinical significance uncertain), and as a partial agonist at the opioid-receptor-like 1 (ORL-1).[12]

Clinical trials. Several meta-analyses of studies comparing buprenorphine to placebo and methadone for the maintenance treatment of opioid addiction indicate buprenorphine is more effective than placebo and as effective as methadone with both drugs being more effective at higher doses.[13–16] Some studies appear to show that buprenorphine may not be as effective as methadone for patients requiring higher doses of methadone (See Table 5 for a summary of some of the key controlled trials). When reviewing the literature of clinical trials with buprenorphine, it is important to remember that the majority of earlier studies were conducted with a sublingual liquid solution. Because the absorption of this solution is different than absorption of the FDA-approved tablet, exact dosing comparisons cannot be made.

Fewer studies have been conducted on short-term detoxification with buprenorphine. One large, multicenter study with both inpatients and outpatients demonstrated that buprenorphine was clearly superior to clonidine in measures of completion of detoxification and negative urine samples at the end of the detoxification (77% vs 22% in the inpatient condition; 29% vs 5% in the outpatient condition).[25] However, a large proportion of both groups did not complete the out-patient detoxification. Further research is needed to determine the longer-term outcomes of patients detoxified from opioids versus those who remain on buprenorphine maintenance.

Safety. It is estimated that buprenorphine has been prescribed to over 100,000 people in the United States[7] and close to 200,000 worldwide.[26] It is very well tolerated with side effects similar to other opioids though tending to be less severe and seen less often. The most common side effects include constipation, headache, nausea, urinary retention, and sedation.[27] Although a decrease in respiratory rate may be observed, this is generally not clinically significant.[28] There are reports of fatal overdose involving buprenorphine and benzodiazepines.[29,30,31] These reports have all come from Europe (where the buprenorphine/naloxone combination is not used) and generally involved individuals who appear to have injected benzodiazepines with dissolved buprenorphine tablets. Although there are no reports of significant buprenorphine overdoses when taken orally or sublingually, buprenorphine should be used with caution in individuals who have a history of benzodiazepine misuse.

Mild elevation in liver enzymes (AST and ALT) has been reported in patients receiving buprenorphine,[27,32] though the clinical significance of this is uncertain. There is also a report of hepatitis following intravenous misuse of buprenorphine.[33] Because of this potential effect on liver enzymes, it is recommended that liver function tests be monitored periodically during the course of treatment with buprenorphine.

Since buprenorphine is metabolized primarily via the cytochrome p450 3A4 system, there is potential for interaction with medications that induce or inhibit this pathway. Common inducers of this enzyme include phenytoin, phenobarbital, carbamazepine, rifampin, afavirenz, and nevirapine. Common inhibitors include fluconazole, erythromycin, indinavir, ketoconazole, metronidazole, ritonavir, and saquinavir. With the exception of a few studies with protease inhibitors (see "Patients with HIV infection" in the "SPECIAL POPULATIONS" section below), very little research has been done to formally assess the extent of drug-drug interactions with buprenorphine. Clinicians should be aware of the potential for interactions with other medications metabolized by the

TABLE 4: Requirements to become qualified to prescribe buprenorphine

The physician has the capacity to refer patients for counseling and ancillary services. The physician is licensed under state law and meets at least one of the following requirements:

1. **Board certification in addiction psychiatry**
2. **Certification in addiction medicine from the American Society of Addiction Medicine (ASAM)**
3. **Board certification in addiction medicine from the American Osteopathic Association (AOA)**
4. **Completion of at least eight hours in the treatment and management that is provided by the ASAM, AOA, the American Medical Association, the American Academy of Addiction Psychiatry, or the American Psychiatric Association.**
5. **Participation in the clinical trials leading to the approval of buprenorphine**
6. **Training or experience deemed sufficient by the physician's state licensing board**
7. **Training or experience deemed sufficient by the Secretary of Health and Human Services.**

TABLE 5: Randomized controlled trials of buprenorphine as a maintenance treatment

TYPE OF STUDY	# PTS	RANDOMIZATION GROUPS				OUTCOMES
Double-blind double-dummy randomized trial[17]	162	Bup 8mg/day sublingual liquid	Methadone 20mg/day (low dose)	Methadone 60mg/day (high dose)		Retention in the program and percent negative urines. At the end of 17 weeks, 42% of the buprenorphine patients remained in the program vs 20% and 32% of low and high methadone patients. Urine screening showed similar results with the buprenorphine group having more negative urines than those in the methadone group.
Double blind randomized trial[18]	140	Bup 2mg/day Sublingual liquid	Bup 6mg/day Sublingual liquid	Methadone 35mg/day Methadone 65mg/day		The 6mg buprenorphine dose reduced illicit opioid use better than the 2mg dose but was not associated with better retention. Both methadone doses were associated with better retention than either buprenorphine dose.
Double blind double-dummy randomized trial[19]	162	Bup 8-16mg/day flexible; sublingual liquid	Methadone 50–90mg/ day flexible			Buprenorphine and methadone were equal in measures of treatment retention (56%) and counseling attendance. They had similar effects on opiate positive urines.
Double blind randomized trial[20]	225	Bup 8mg/day sublingual liquid	Methadone 30mg/day	Methadone 80mg/day		The 8mg/day buprenorphine dose was less effective than the 80mg methadone dose for treatment retention and negative opioid urines. It was comparable to the 30mg methadone dose.
Double blind randomized trial[21]	116	Bup 4mg/day sublingual liquid	Bup 12mg/day sublingual liquid	Methadone 20mg/ day	Methadone 65mg/ day	Both higher methadone and buprenorphine groups had better negative urine opioid positive results (45%, 58% vs 72%,77%). Treatment retention was similar in all groups.
Multi-site double-blind random trial[22]	736	Bup 1mg/day sublingual liquid	Bup 4mg/day sublingual liquid	Bup 8mg/day sublingual liquid	Bup 16mg/day sublingual liquid	The 8 and 16mg groups had significantly better rates of treatment completion. There was more sustained abstinence in the 16mg group.
Double blind randomized trial[23]	106	Bup 16mg/day tablet	Placebo			Retention in treatment was significantly better for the buprenorphine group (30%) than the placebo group (2%).Reported opioid use was significantly lower in the buprenorphine group.
Randomized control trial[24]	220	Bup 16–32mg 3 times/week	LAAM 75–100mg 3 times/week	High dose Meth 60–100mg/day	Low dose Meth 20mg/day	Retention in treatment and negative urine toxicologies at the end of 17 weeks. The mean retention time was 96.4±4 days for bup group, 89±6 days for the LAAM group , 105±4 days for the high dose methadone group and 70±4 days for the low dose methadone group. The percent of patients with twelve or more consecutive opioid negative urines was 26, 36, 28 and 8 for bup, LAAM, high and low methadone dose, respectively. The authors concluded that buprenorphine, LAAM and high dose methadone substantially reduced illicit opioid use compared to low dose methadone.

cytochrome p450 3A4 system and talk with patients about the possible effects on buprenorphine levels.

Formulations and costs. Buprenorphine is currently available in the US in three formulations (Table 6). A transdermal product has been approved and marketed in Europe.[34] A long-acting, depot formulation is also under development.[35,36] Buprenex is a liquid form administrated intramuscularly or intravenously for pain management. Subutex is a sublingual tablet used for opioid addiction. Suboxone is a formulation that contains buprenorphine and naloxone in 4:1 ratio. Naloxone, an opioid antagonist, was added to deter injection of dissolved pills, thus reducing abuse liability and the potential for diversion. Because naloxone is poorly absorbed sublingually, its effect when

Suboxone is taken properly is minimal. However, if the tablet is dissolved and injected, the naloxone blocks mu receptors and prevents receptor activation or precipitates withdrawal in opioid dependent patients.

A 30-day supply of an average dose of Suboxone (two 8/2mg Suboxone tablets per day) costs approximately $287.50 from a retail pharmacy.[37] Subutex is slightly more expensive than Suboxone. This is to discourage the use of Subutex, which has a higher potential for abuse.

Dosing. Maintenance treatment of opioid addiction with buprenorphine can be divided into the following three phases: 1) induction, 2) stabilization, and 3) maintenance.[38]

The induction phase generally entails the initial transition from illicit opioid use to buprenorphine, typically lasting from 3 to 7 days. Patient education is extremely important with emphasis on the risk of precipitated withdrawal if buprenorphine is initiated too soon after last opioid use (generally 12–24 hours for short-acting opioids and 24–48 hours for long-acting). Patients should also be advised to not drive or operate machinery until the effects of buprenorphine have been determined and the dose stabilized. For initiation, it is recommended to use Suboxone (combination tablet) for the majority of patients. Exceptions include pregnant women who are deemed appropriate for buprenorphine and some patients who are using long-acting opioids, such as methadone, in which case Subutex may be used initially. In the latter case, the patient should be switched to Suboxone after the first day.

After it has been determined that the patient is exhibiting signs of opioid withdrawal (Table 2), the initial doses of buprenorphine, usually 4/1mg of the buprenorphine/naloxone tablet (2mg if patient dependent on long-acting opioid) should be administered under direct observation by the physician. Over the next several hours, the patient should be monitored for both precipitated withdrawal and excessive opioid agonist effects, such as sedation. If, after two hours, the patient continues to exhibit signs of opioid withdrawal, another dose of 4/1mg Suboxone can be administered. If the patient is dependent on long-acting opioid, 2mg can be administered every 1 to 2 hours. The total recommended dose of buprenorphine for the first day is 8mg. If the patient continues to complain of some symptoms of withdrawal, other symptomatic treatments can be provided.

On the second day of induction, the extent of withdrawal should be determined. If the patient reports no symptoms of withdrawal, the total dose from the first day should be repeated and the patient should remain on that daily dose. If the patient reports symptoms of opioid withdrawal, 4/1mg in addition to the total dose from the first day should be administered. Subsequent dose increases of 2/0.5 or 4/1mg may be administered to a total dose of 16mg of buprenorphine.

Over the subsequent days of the induction phase, the above procedure should be repeated to a maximum dose of 32/8mg per day by the end of the first week. If the patient continues to complain of opioid withdrawal, illicit opioid use should be suspected. If the patient continues to struggle with opioid use, increased psychosocial intervention is likely to be necessary.

The stabilization phase generally lasts 1 to 2 months and is a period of adjusting the medication to establish the minimum dose required to eliminate withdrawal symptoms, reduce opioid craving, and minimize side effects. For most patients, this will be achieved at a daily dose of 12/3 to 24/6mg of Suboxone per day. Some patients may require 32/8mg per day. Frequent contact with the patient may be necessary during this period to facilitate dose adjustment and enhance adherence. The need for further psychosocial addiction treatment should continue to be assessed during this period. Some evidence suggests that, with a

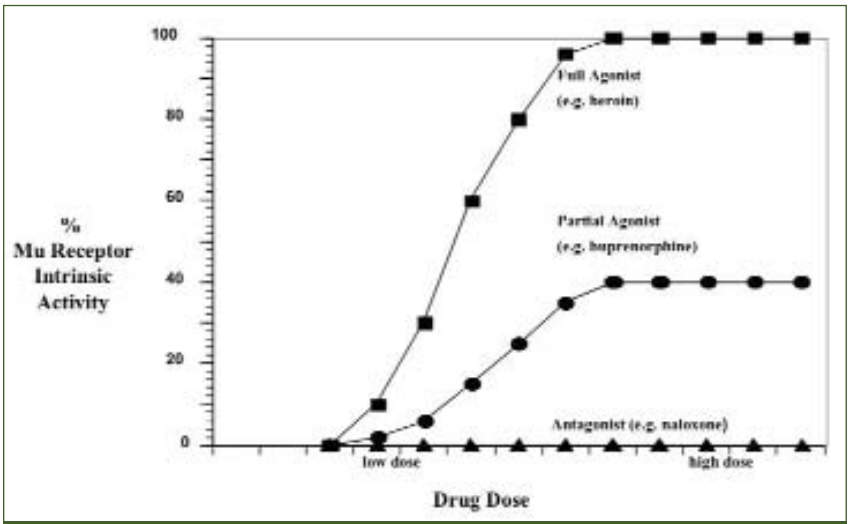

FIGURE 1: Mu Opioid Receptor Activation

TABLE 6: Available formulations of buprenorphine				
TRADE NAME	**ROUTE OF ADMINISTRATION**	**INDICATION**	**DESCRIPTION**	**AVAILABLE STRENGTHS**
Subutex	**Sublingual**	**Opioid maintenance and detoxification**	**White oval tablet with sword inlay**	**2mg, 8mg**
Suboxone (combination buprenorphine and naloxone)	**Sublingual**	**Opioid maintenance and detoxification**	**Orange hexagonal tablet with sword inlay**	**2mg (with 0.5mg naloxone 8mg (with 2mg naloxone)**
Buprenex (also available as a generic)	**Intravenous Intramuscular**	**Pain management**	**Liquid**	**0.3mg/mL**

16mg sublingual dose, it may be possible for patients to take buprenorphine every other day.[39,40]

The maintenance phase is indefinite and must be determined individually with each patient, taking into consideration his or her specific goals of treatment. During this period, it is important that the physician continue to monitor the patient for illicit drug use, cravings, and triggers to relapse. It is also important to insure that psychosocial issues are being addressed, either within the physician's practice or by other counseling or self-help mechanisms. The decision to discontinue buprenorphine must be carefully discussed with each patient. A plan for dealing with relapse should be defined.

For detoxification, Suboxone or Subutex may be used. The initial dose is generally 4 to 8mg of buprenorphine with 2 to 4mg as needed for additional signs and symptoms of withdrawal. Twice per day dosing may be preferable during acute detoxification. The dose is then tapered over a variable amount of time (days to weeks). The physician is not limited to the 72-hour, directly observed dispensing that is required with the use of other opioids for detoxification.

For patients admitted to a general hospital for a condition other than opioid dependence specifically, buprenorphine can be used to manage opioid withdrawal while the other condition is being treated. In this specific situation, the prescribing physician does not need to have their federal buprenorphine waiver. Similar doses to those used in outpatient detoxification may be used. Higher and more frequent doses may be more effective in managing concomitant, mild to moderate pain, such as that experienced with cellulites or an abscess.

Special populations.

Pregnant patients. Infants exposed to opioids *in utero*, whether illicit or prescribed, typically show signs of withdrawal after birth. This withdrawal is referred to as the neonatal abstinence syndrome (NAS). Methadone maintenance has been shown to improve maternal and newborn outcomes in pregnant opioid dependent patients.[41] A review of the current literature suggests that maintenance with buprenorphine may also improve maternal and fetal outcomes and that the resultant NAS may be less intense than that seen with methadone.[42,43] Buprenorphine is currently a Category C drug in pregnancy. There is more evidence to support the use of methadone, which is Category B, in pregnant patients. If methadone is unavailable and it is deemed necessary to treat with buprenorphine, the risks and benefits should be explained to the patient and Subutex, not Suboxone, should be used.

Breast feeding patients. Although the data are limited, it is clear that buprenorphine does pass into the breast milk of lactating women.[44] Because of the poor oral bioavailability, it is not clear how much of this buprenorphine is absorbed by the nursing infant. Limited clinical reports appear to show that NAS is not suppressed by the presence of this buprenorphine and that NAS does not generally develop when breast feeding is stopped.[43,45] Although the Suboxone and Subutex package inserts advise against breast feeding while taking buprenorphine, the apparently minimal effect on the infant may not necessitate discontinuation of the medication. Further research should help clarify this issue.

Adolescent patients. Although the use of

buprenorphine has not been systematically studied in this population, it is reasonable to consider it as a first-line pharmacologic treatment after detoxification and "drug-free" treatment has been attempted. Rules concerning the need for parental consent for an adolescent to receive addiction treatment vary from state to state. It is important for any physician considering the use of buprenorphine in an adolescent to be thoroughly familiar with the appropriate laws in his or her state. It is also useful to have some knowledge of treatment resources available for adolescents as these are often different than those available for adults.

Geriatric patients. There is no specific literature addressing the use of buprenorphine in elderly patients. Because of the potential differences in absorption, distribution, and metabolism, caution should be exercised in elderly patients, especially during the induction phase. Potential medication interactions should be considered.

Patients with HIV infection. HIV infection is a common comorbid condition with opioid dependence. Buprenorphine has the potential to both help prevent HIV transmission and improve the adherence with treatment in patients already infected with HIV.[46] The current standard of care for HIV infection is highly active antiretroviral therapy (HAART). One study examined the use of buprenorphine for opioid-dependent patients taking HAART. It concluded that patients receiving buprenorphine were more likely to adhere to the HAART regimen than untreated opioid dependent patients[47] and that buprenorphine had no impact on the virologic response to HAART.[48]

Protease inhibitors have the potential to interfere with buprenorphine metabolism by inhibiting activity of the cytochrome p450 3A4 enzyme. An *in-vitro* study found that ritanavir, idinavir, and saquinavir all inhibited dealkylation of buprenorphine.[49] Another study reported a lack of interaction between buprenorphine and zidovudine.[50] Until further research is done, clinicians should monitor patients for signs and symptoms of opioid intoxication and withdrawal when using antiretroviral medications. The dose of buprenorphine may need to be adjusted.

Patients with viral hepatitis infection. Hepatitis C is another common condition associated with opioid dependence. Since buprenorphine is metabolized in the liver, patients with hepatitis should have liver function monitored while on therapy. Patients should be cautioned that intravenous use has been associated with significant liver damage.[32]

Patients with pain. Two of the pharmacologic properties of buprenorphine contribute to potential difficulties in pain management with patients maintained on buprenorphine. The fact that buprenorphine is a partial agonist at the mu opioid receptor means that its analgesic effects have a ceiling effect. The fact that it has a very high binding affinity for these receptors means that it will typically prevent binding of other full mu agonists used to treat pain. Despite these potential concerns, there is a paucity of research in this area.

Various options exist for management of acute pain in the buprenorphine-maintained patient. Initially, nonopioid medications such as ketorolac or NSAIDs can be added to the regular dose of buprenorphine. If pain persists and the patient is on a lower dose of buprenorphine (below 24–32mg per day), the dose can be increased for additional analgesic effect. Other non-opioid options might include the use of regional anesthesia, conscious sedation with a benzodiazepine, or general anesthesia.

If the pain is not improving with these measures, the decision may be to discontinue buprenorphine and initiate opioid agonist therapy. Initially, the dose of the full opioid agonist required may be greater than usual; higher doses of a full agonist opioid may overcome the blockade caused by buprenorphine. A rapidly acting opioid analgesic, which minimizes the duration of respiratory depression, should be used. The dose of opioid medication should be titrated against the patient's analgesic

SOURCES OF INFORMATION on buprenorphine and buprenorphine training courses

The Center for Substance Abuse Treatment
http://buprenorphine.samhsa.gov

American Psychiatric Association
www.psych.org

American Society of Addiction Medicine
www.asam.org

American Academy of Addiction Psychiatry
www.aaap.org

American Osteopathic Association
www.aoa-net.org

Food and Drug Administration
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and physiological response, with close monitoring for respiratory depression.

In the case of elective surgery, the physician may titrate the buprenorphine dose down and transfer the patient to a full opioid agonist prior to surgery. Afterward, the full agonist can be discontinued and buprenorphine may be titrated back up to the therapeutic level. Communication between providers is crucial to the success of this.

Management of chronic pain in the buprenorphine-maintained patient is likely to be best accomplished by consultation with a specialist in pain medicine with possible referral to a multidisciplinary pain program. The site of such treatment will depend on the patient's specific needs and the goals of treatment. Alternative methods of pain control, such as TENS, may be suitable for some patients.

Although the sublingual formulations of buprenorphine are not approved by the FDA strictly for pain management in non-addicted individuals, a growing body of literature is becoming available that supports the potential role of these medications as analgesics.[26,51]

SUMMARY

Opioid addiction is a significant problem in the United States. For nearly a century, Federal regulations have made it impossible for physicians to manage opioid addiction in an office setting. The Drug Addiction Treatment Act makes it possible for psychiatrists to manage all aspects of their patients' mental health, including opioid dependence, with a safe, efficacious, and well-tolerated medication.

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Although the use of buprenorphine has not been systematically studied in the adolescent population, it is reasonable to consider it as a first-line pharmacologic treatment after detoxification and "drug-free" treatment has been attempted.

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